

**ABSTRACT OF THE DISCLOSURE**

The present invention concerns methods and nucleic acid based reagents useful in modulating gene expression in a variety of applications, including use in therapeutic, veterinary, agricultural, diagnostic, target validation, and genomic discovery applications. Specifically, the invention relates to double strand forming oligonucleotides (DFO) that can self assemble to form double stranded oligonucleotides, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA) molecules, and modulate gene expression, for example by RNA interference (RNAi). The self complementary DFO nucleic acid molecules are useful in the treatment of any disease or condition that responds to modulation of gene expression or activity in a cell, tissue, or organism.